

PSJ2 Exh 84



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

William A. Best, Sr.
Director, Promotional Regulatory Affairs
Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

RE: NDA #201655
OPANA[®] ER (oxymorphone hydrochloride) Extended-Release tablets, CII
MA #7

Dear Mr. Best:

This letter responds to Endo Pharmaceuticals, Inc.'s (Endo) February 29, 2012, request to the Division of Professional Drug Promotion (DPDP) for comments on a launch Draft Professional Detail Aid – PSA (OP-01970) (detail aid) for OPANA[®] ER (oxymorphone hydrochloride) Extended-Release tablets, CII (Opana ER).

DPDP, in consultation with the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), has reviewed the proposed detail aid and offers the following comments. These comments should be applied to this submission and all current and future promotional materials for Opana ER that contain the same or similar claims or representations.

General

DPDP reminds you that terms such as “new” and “introducing” should only be used for six months after the date Opana ER is initially marketed. After that six month period of time, materials containing these terms should be revised or replaced.

We remind you that DPDP does not provide advisory comments on claims and presentations which are the same or similar to those in the public domain. Therefore, DPDP's comments are limited to those claims and presentations not currently disseminated in the public domain.

Minimization of Risk Information/Implied Unsubstantiated Safety Superiority Claims

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is safer than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience.

The proposed detail aid contains numerous claims and presentations describing Opana ER's new formulation and its INTAC[™] technology. For example, page two includes claims such as the following (bolded emphasis original; underlined emphasis added):

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- **“INTAC™ technology provides mechanical stability”**
- “Innovative manufacturing process uses heat extrusion to create mechanical strength” (page 2)
- “New formulation of Opana® ER tablets with INTAC technology has the mechanical strength to provide an obstacle to crushing by tools, including hammers, spoons, and mechanical pill crushers”

Additionally, page three includes claims and presentations such as the following regarding a blinded comparative study in 25 subjects (bolded emphasis original):

- **“Opana® ER with INTAC™ technology compared to oxymorphone ER (original formulation). . . Provided some resistance to crushing by tools, including spoons, a hammer, or a razor”**
- **“Manipulating Opana® ER tablets with INTAC™ technology resulted in larger particle size than oxymorphone ER (original formulation)”** (with accompanying visual)
- **“Study demonstrated the difficulty in forming an intranasal preparation”** (with accompanying visuals)

The totality of these claims and presentations suggest that, as a result of its new formulation, Opana ER offers a therapeutic advantage over the original formulation when this has not been demonstrated by substantial evidence or substantial clinical experience. In addition, these claims misleadingly minimize the risks associated with Opana ER by suggesting that the new formulation’s “INTAC™ technology” confers some form of abuse deterrence properties when this has not been demonstrated by substantial evidence. Although we acknowledge that there is evidence to support some limited improvement in mechanical stability and strength attributable to the new technology as well as a minimal improvement in resistance to tampering in efforts to abuse Opana ER intranasally, there are several limitations to this data. Furthermore, Opana ER’s approved product labeling (PI) has a Boxed Warning which contains the following information (in pertinent part; bolded emphasis original):

WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE

...

Potential for Abuse

OPANA ER contains oxymorphone, which is a morphine-like opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.

...

Limitations of Use

OPANA ER tablets are to be swallowed whole and are not to be cut, broken, chewed, dissolved, or crushed. Taking cut, broken, chewed, dissolved, or crushed OPANA ER tablets leads to rapid release and absorption of a potentially fatal dose of oxymorphone.

We acknowledge that the proposed detail aid presents statements such as, “The clinical significance of INTAC technology or its impact on abuse/misuse has not been established for

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the new formulation of Opana ER” on various pages of the piece; however, these and similar statements do not mitigate the overwhelming misleading impression. Therefore, DPDP recommends that these claims and presentations regarding Opana ER’s new formulation be deleted from the proposed detail aid. We are especially concerned from a public health perspective because the presence of this information in the detail aid could result in health care practitioners or patients thinking that the new formulation is safer than the old formulation, when this is not the case. If Endo wishes to have this data further evaluated to support a labeling change or wishes to pursue further discussions regarding the tamper resistance properties of Opana ER, DPDP refers you to the Division of Anesthesia, Analgesia, and Addiction Products within the Office of New Drugs.

Omission of Material Facts

Promotional materials are false or misleading if they fail to reveal facts with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

Page one of the proposed detail aid presents information from the Indications and Usage section of the PI. This presentation is misleading because it omits the following information from the Indications and Usage section of the full PI:

1 INDICATIONS AND USAGE

...

Limitations of Use

...

OPANA ER is only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate or severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate.

We recommend revising the proposed detail aid to prominently present Opana ER’s full indication in conjunction with the initial claims of efficacy. We note that this information is communicated on page three under the header “CONTRAINDICATIONS;” however this does not mitigate this misleading omission.

In addition, the proposed detail aid omits the following important risk information from the PI (in pertinent part) (bolded emphasis original; underlined emphasis added):

5.2 Respiratory Depression

...

Administer OPANA ER with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma.

5.3 Misuse, Abuse and Diversion of Opioids

...

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Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion

OPANA ER tablets may be abused by crushing, chewing, snorting, or injecting the product. These practices will result in the less controlled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death

Healthcare professionals should advise patients to store OPANA ER in a secure place, preferably locked and out of the reach of children and other non-caregivers.

5.5 Use in Patients with Head Injury and Increased Intracranial Pressure

In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO₂ retention) may be markedly exaggerated. Furthermore opioid analgesics can produce effects on papillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Administer OPANA ER with extreme caution to patients who may be particularly susceptible to the intracranial effects of CO₂ retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

5.9 Gastrointestinal Effects

OPANA ER decreases bowel motility. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of OPANA ER may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

5.10 Ambulatory Surgery and Post-Operative Use

Patients who are already receiving OPANA ER as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention.

We recommend revising the proposed detail aid in order to include the important material information that is underlined above.

If you have any questions or comments, please direct your response to the undersigned by facsimile at (301) 847-8444, or at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. Please note that the Division of Drug Marketing, Advertising, and Communications

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(DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and the Division of Consumer Drug Promotion (DCDP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA #7 in addition to the NDA number in all future correspondence relating to this particular matter. DPDP reminds you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Samuel M. Skariah, Pharm.D.
LCDR, USPHS
Regulatory Review Officer
Division of Professional Drug Promotion
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAMUEL M SKARIAH
04/30/2012